83-790688/42 B04 D16 J04 K08 INSP 12.03.82
INST PASTEUR (CNRS) *FR 2523-311-A
12.03.82-FR-004247 (16.09.83) G01n 33/68 C07g 07/00

Aq.- soluble albumin-ligand coupling product - for use in immunoassays

C83-102376 Issued in Week 8343.
Full Patentees: Inst. Pasteur; Cent. Nat. Rech. Scientifique.

(A) an albumin/specific ligand coupling prod. which is soluble in aq. media is new.

(B) Immunoassay of a biological substance (I) comprises (a) immobilising a substance (II) having binding affinity for (I), (b) incubating with a medium contg. (I), (c) washing the resulting reaction mixt. and incubating with an albumin/specific ligand coupling prod. in soln. in an aq. medium, where the ligand is capable of reacting specifically with (I) or (II), (d) washing the resulting reaction mixt.and incubating with a labelled anti-albumin antibody, and (e) detecting the label.

(C) An immunoassay test kit comprises an albumin/specific ligand coupling prod., a labelled anti-albumin antibody and reagents for detecting the label.

ADVANTAGES

Coupling with albumin increases sensitivity, esp. in the case of enzyme immunoassays for antigens, haptens or antibodies.

DETAILS

The specific ligand may be an antigen, hapten, antibody, hormone, hormone receptor, enzyme inhibitor or lectin. It may be coupled with human or animal albumin (esp. BSA) using glutaraldehyde or by 2-stage benzoquinone activation and coupling.

The label may be an enzyme, a radioactive material, a fluorochrome, a particulate material or erythrocytes.

EXAMPLE

A BSA/anti-IgE reagent was prepd. by isolating sheep anti-rabbit Ig antibodies by affinity chromatography, dialysing the antibodies and BSA against phosphate buffer (0.1 M, pH 6.8) at 4°C overnight, and mixing 3 mg of the dialysed antibody with 6 mg of the dialysed BSA in 0.1M phosphate buffer. The mixt. (1 ml) was treated with 0.2 ml of 1% aq. glutaraldehyde and incubated at room temp. for 3 hr.

The prod. was used in a sandwich-type enzyme immunoassay for human IgE.(18pp367EDDwgNo0/0).

FR 2523311-A

B(4-B2C, 4-[illegible]D, 4-B4A, 4-B4C, 4-B4D, 4-B4F, 5-A4, 11-G7A, 11-C7B, 12-K4) D(5-A1, 5-H) J(4-B1) K(9-B, 9-E), 10 001

83-795400/43 B07 P34 HEYM/ 01.03.82
HEYMAN A M *AU 8311-382-A
18.05.82-US-379480 (+US-353432) (08.09.83) A61m-29

Urological instrument esp. retentive balloon catheter - inserted by sliding over filiform

C83-102379 A urological instrument (esp. a catheter) is inserted into the bladder by first advancing a filiform through the urethra, the filiform having smoothly contoured leading end with a lateral opening. Urine flows through this opening and into the filiform to indicate when the leading end of the filiform has entered the bladder.

The urological instrument has an internal dia. greater than the external dia. of the filiform to permit the instrument to be slid along the filiform. The instrument may have an inflatable balloon collar which retains the instrument in the bladder; the filiform can then be withdrawn.

ADVANTAGE

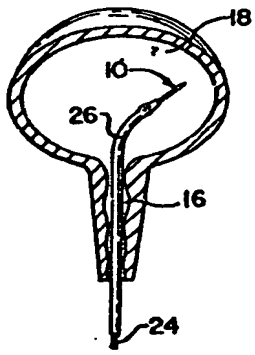
The correct positioning of the filiform is indicated by the drainage of urine.

EMBODIMENT

Bladder (18) has the drainage catheter (26) in position.

Pref. the leading section of the filiform (10) is curved as shown.

The filiform may be inserted while a stylet wire extends axially within the filiform to stiffen it. Similarly, a stylet tube (24) is placed inside the drainage catheter while it is being slid along the pre-positioned filiform.(25pp295GHDwgNo5/6)



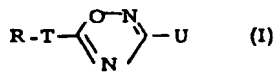

AU 8311382-A

B(11-C4B) 002

83-795403/43 B03 (B02) SUMO 03.03.82
SUMITOMO CHEMICAL KK *AU 8311-483-A
03.03.82-JP-034168 (08.09.83) A61k-31/41 C07d-271/06 C07d-413/04 C07d-417/10 C07d-471/04 C07d-491/05

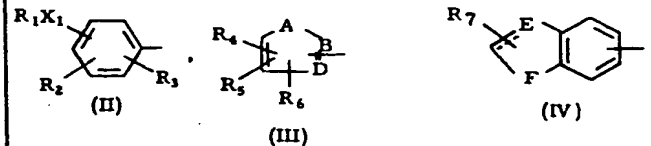
5-Aralkyl-1,2,4-oxadiazole derivs. - are antiinflammatories, analgesics and antipyretics

C83-102382 5-Aralkyl-1,2,4-oxadiazole derivs. of the formula (I) and their salts are new




(I)

(R is a gp. of formula (II), (III), (IV) or (V):




(II) (III) (IV)

B(6-H, 7-E4, 12-D1, 12-D7, 12-D8) 003


(V) (VI)

$R_1$ is alkyl, alkenyl, cycloalkyl, cycloalkenyl, opt. substd. phenyl or heterocyclyl;
$R_2$ and $R_3$ are each H, halo, amino, OH, alkoxy or alkyl;
$X_1$ is $-CH_2-$, $-CH_2O-$, $-CO-$, $-O-$, $-S-$, $-NH$ or a single bond;
$R_4$ and $R_5$ are H, alkyl or opt. substd. phenyl;
$R_6$ is opt. substd. phenyl or opt. substd. benzoyl;
A is N, O or S;
B and D are each C or N;
$R_7$ is alkyl, lower alkoxy or opt. substd. phenyl;
E is N or C;
F is O, S or C or C=C or C=N,
broken lines indicate opt. bonds;
$R_8$ is H or lower alkyl;

AU 8311483-A



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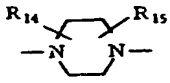
$R_9$ is H, halo or alkoxy;
$R_{10}$ is H, cyclohexyl or substd. benzoyl;
G is methylene, substd. benzoylimino, cinnamoylimino or substd. styrylidene, provided that G is $-CH_2-$ when $R_{10}$ is cyclohexyl or substd. benzoyl;
$R_{11}$ is H, halogen, alkyl or alkoxy;
$X_2$ and $X_3$ are different and are $-CH_2-$, -CO-, -O-, -S-, -NH- $-N(CH_3)-$ or single bond;
J is a benzene, pyridine, thiophene, furan or pyrrole ring;
n is 0 or 1;
T is alkylene or alkenylene each opt. carrying an oxo, OH or lower alkoxy substit., or T is a single bond;
U is H, alkyl, alkenyl, polyhaloalkyl, cycloalkyl, cycloalkenyl, opt. substd. phenyl, pyridyl, $-T_1-R_{12}$ or $R_{13}-X_4-T_2-$;
$R_{12}$ is halogen, OH, SH, alkylsulphinyl, dialkoxymethyl, alkoxycarbonyl, COOH, sulpho, CN, NR'R" or $-\oplus SR_1'R_1''.X\ominus$;
R' and R" are H, alkyl or hydroxyalkyl;
or NR'R" forms a 5 or 6 membered opt. unsatd. heterocyclic ring, which may contain an O or another N atom, or forms a quaternary ammonium salt or N-oxide;
$R_1'$ or $R_1''$ are alkyl or alkenyl;
X is negative monovalent ion;
$T_1$ is alkylene or alkenylene, opt. bearing an OXO or OH substit.;
$R_{13}$ is alkyl, alkenyl, hydroxyalkyl, acyloxyalkyl, aminoalkyl, acylaminoalkyl, cycloalkyl, cycloalkenyl, opt. substd. phenyl, phenyl-alkyl, heterocyclyl, heterocyclyl-alkyl, acyl, acylthioalkanoyl, mercaptoalkanoyl, alkoxycarbonyl, alkylsulphonyl, $-CONR_2'R_2''$ or $SO_2NR_2'R_2''$;
$R_2'$ and $R_2''$ are each H, alkyl or hydroxyalkyl;
$X_4$ is -O-, -S-, -NH-, a single bond or a gp. of formula (VIII)



(VIII)

$R_{14}$ and $R_{15}$ are each H or alkyl.
All alkyl, alkenyl, alkylene, alkenylene, cycloalkyl and cycloalkenyl gps. are 'lower' i.e. ≤ 6C; and cycloalkyl gps. may be oxo- or hydroxy-substd.).

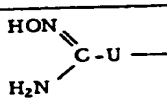
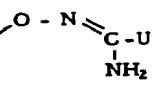
USE

(I) are antiinflammatories, analgesics and antipyretics without ulcerogenic side effects.

PREPARATION

By several methods including:-

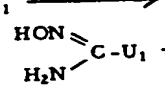
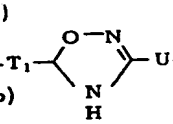
AU8311483-A

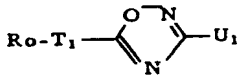
1) R-T-COOH + (or reactive ester) (II) +  (III) →  (IV) → (I)

2) R-T-CN + $O\leftarrow N\equiv C-U_1$ → (I; U = $U_1$)
(V)

($U_1$ is alkyl, alkenyl, polyhaloalkyl, cycloalkyl, cycloalkenyl, phenyl, substd. phenyl, pyridyl or $R_{16}-T_2-$;
$T_2$ is alkylene or alkenylene;
$R_{16}$ is halogen, alkoxy, alkenyloxy, dialkoxy) methyl carboxy, cycloalkyl, phenyl, substd. phenyl, pyridyl, NR'R", $CONR_2'R_2''$ or $-SO_2NR_2'R_2''$).

3) R-T-CONHCSU$_1$ $\xrightarrow{H_2NOH}$ (I; U = $U_1$)

4) RO-$T_1$-CHO +  →  (Ib)

oxidn. → 

(Ro is same as R provided $X_1$, $X_2$ and $X_3$ are not -S-)

EXAMPLE

A mixt. of 2-(2-fluoro-4-biphenylyl)propionic acid (2.44 g), dry benzene (50 ml) and thionyl chloride (2.38 g) was refluxed for 2 hr., concd. under reduced pressure and residue dissolved in dry benzene (5 ml). The soln. was added dropwise with cooling to a soln. of acetamidoxime (0.815 g) in dry pyridine and stirred at room temp. and refluxed for 5 hr. The solvent was evapd. under reduced pressure and the residue partitioned between benzene (100 ml) and 10% $Na_2CO_3$ soln. (20 ml). The organic phase was washed, dried and evapd. and the residue chromatographed on silica gel and eluted with benzene to give 5-(3-fluoro-4-phenyl-α-methylbenzyl)-3-methyl-1,2,4-oxadiazole which was recrystallised from n-hexane to give product (m.p. 55-56°C).(99pp916EDDwgNo0/0).

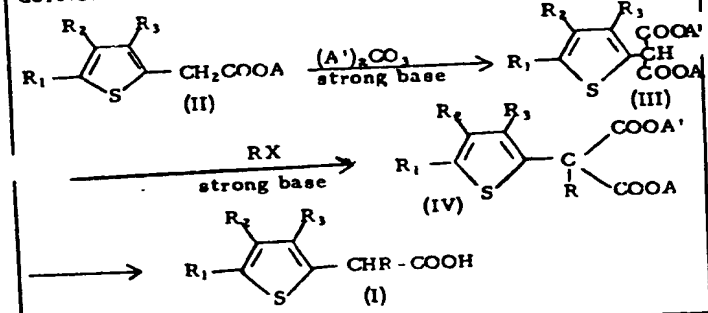
83-795403/43(3) AU8311483-A

83-795432/43 B03 ROUS 03.12.82
ROUSSEL UCLAF *BE -896-439-A
03.12.82-FR-020271 (12.10.83) C07d

Alpha-alkyl 2-thienyl acetic acid derivs. prodn. - by reacting 2-thienyl acetic acid with alkyl carbonate alkylating agent, then decarboxylation

C83-102391

(1) Prodn. of α-alkyl- 2-thienylacetic acid derivs. of formula (I) by the following process is new:



(R is 1-4C alkyl;
$R_1$, $R_2$ and $R_3$ are each H, 1-4C alkyl or halo;
A and A' are 1-4C alkyl; and
X is a functional gp).
(2) The 2-(1,1-di(alkoxycarbonyl)-alkyl)-thiophene intermediates of formula (IV) are new cpds.

USE

(I) are intermediates for pharmaceuticals, esp. antiinflammatories.

ADVANTAGES

The process uses fewer stages than known methods.

DETAILS

The first stage is pref. in presence of Na ethoxide (esp. 1-1.5 equiv. per mole (II)) at 90-135°C. Reaction of (IV is esp. also in presence of Na ethoxide, at 50-80°C.

The final stage is by hydrolysis with base, esp. at 50°C to reflux, then acidification with HCl.

The method is esp. used to make (I) where $R_1$ = $R_2$ = $R_3$ = H and R = methyl, cpd. (Ia).

EXAMPLE

BE 896439 -A

B(7-B1) 1 004

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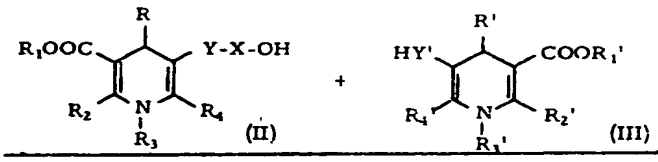
$R_4$ is H, aralkyl, aryl, heteroaryl, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, alkylene, dioxyalkylene, halogen, mono- or polyfluoroalkoxy, mono- or polyfluoroalkyl, OH, $NH_2$, alkylamino, $NO_2$, CN, $N_3$, COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl or $SO_2$-alkyl, the aryl, heteroaryl and alkyl residues opt. mono-, di- or tri-substd. by aryl, alkyl, alkoxy, aralkyl, dioxyalkylene, halogen, mono- or polyfluoroalkyl, mono- or polyfluoroalkoxy, OH, $NH_2$, alkylamino, $NO_2$, CN, $N_3$, COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl or $SO_2$-alkyl).

USE

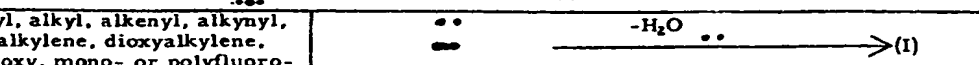
(I) have cardiovascular activity and can be used as antihypertensives, vasodilators, cerebral agents and coronary agents. They have a partic. prolonged duration of action.

PREPARATION

E.g.



(II) + (III)



The reaction is in an inert organic solvent at 0-180°C in the presence of dehydrating agents using equiv. amts. of (II) and (III).

EXAMPLE

2,6-Dimethyl-5-(4-hydroxybutoxy-carbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid ethyl ester (25 mmol), DCC (25 mmol) and 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid (25 mmol) in anhydrous DMF (50 ml) are heated 4 hrs. at 100°C with 4-dimethylaminopyridine (0.2 g), then worked up to give 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid 1,4-butanediyl ester as an amorphous foam in 25% yield.(53pp280).

(G) ISR: DE2847236 DE1795791 DE2117571

EP--52300

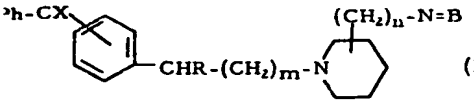
4121 E/22 803 STER 19.11.80
TERLING DRUG INC *EP--52-311
24.08.81-US-297759 (+208259) (26.05.82) C07d-211/26
l-Benzoyl-phenyl-alkyl-piperidine derivs. and analogues - useful as ronchodilators, anti:asthmatics, anticholinergics

B(7-D5, 12-D2, 12-E4, 12-G1, 12-K2) 5

34

)/S: E(BE CH DE FR GB IT LI LU NL SE).

4(Benzoylphenylalkyl)piperidine derivs. and analogues of ormula (I) and their acid-addn. salts are new.



(I)

R is H or 1-6C alkyl;
n is 0 or 1;
is 0 or 1;
I=B is 1-piperidinyl, 4-morpholinyl, $NH_2$, di-(1-6C)alkylmino, 1-6C alkanoylamino, N-(1-6C)alkyl-N-(1-6C)alkanylamino, cycloalkanecarbonylamino, or PhCONH opt. ring ubstd. by 1-6C alkyl, halogen or 1-6C alkoxy;
:X is CO or CH(OH);

PhCX is attached to the 3- or 4-posn. when m is 1 or only to the 3-posn. when m is 0;
provided that when m is 0, n is 1, R is alkyl and N=B is 1-piperidinyl or 4-morpholinyl).

USES

(I) are bronchodilators, antiasthmatics, antiallergics, anticholinergics and prostaglandin synthetase inhibitors.

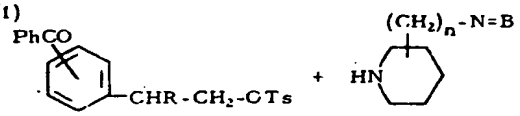
SPECIFICALLY CLAIMED

8 Cpds. (I), including 1-(2-(3-benzoylphenyl)propyl)-4-acetylaminopiperidine HCl and the corresp. 4-benzoyl cpd.

PREPARATION

Methods used include:

(1)

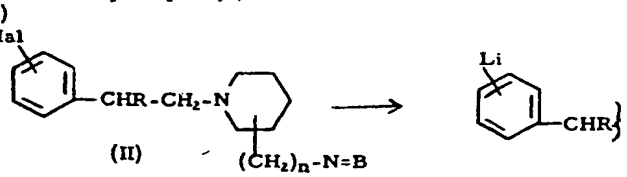


acid acceptor → (I, m is 1, CX is CO)

EP--52311

s is toluene-p-sulphonyl).

(2)



1) Benzonitrile
2) Hydrolysis → (I; m is 1, CX is CO)

(3) When m is 1, redn. of a corresp. ketone, i.e. with a HR-CO- bridge, with $LiAlH_4$ gives the prod. When CX is O, it may be protected by ketalisation etc.

XAMPLE

10.17g α-(3-benzoylphenyl)propionic acid in 25 ml benene was treated with 9.52g $SOCl_2$ and refluxed for 3.25 hrs. he mixt. was evapd. and the residual oil in 25 ml $CH_2Cl_2$ as added to 4.86g $NEt_3$ and 7.29g 4-(1-piperidinylmethyl)-iperidine over 15-20 mins. at about 5°C. The mixt. was tirred for 3 hrs., washed with water, aq. $NaHCO_3$ and aq. aCl, filtered and evapd. to give 1-(α-(3-benzoylphenyl)-propionyl)-4-(1-piperidinylmethyl)piperidine as an oil. It formed a HCl salt, m.p. 211-212°C.(42pp1248).

(E) ISR: GB1250719 US3816434 GB1508391 FR1549342 US4216326.

EP--52311

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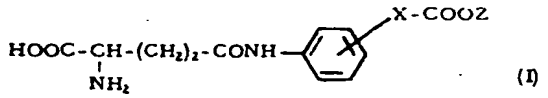
4111 E/22 B05 MITU 12.11.80
MITSUBISHI CHEM IND KK (NNSH) *EP--52-296
12.11.80-JP-159320 (+159319) (26.05.82) A61k-37/02 C07c-103/52

**lutamine derivs. - useful as immuno:modulating agents with mmunosuppressive and immunostimulating activities**

D/S: E(AT BE CH DE FR GB IT LI NL SE)
Full Patentees: Mitsubishi Chem. Ind. Ltd. and Nippon Shinyaku Co. Ltd.

Glutamine derivs. of formula (I) and their salts are new.



(I)

X is $(CH_2)_n$, vinylene or $CR_1R_2$;
n is 1-4;
$R_1$ and $R_2$ are each H or 1-4C alkyl, at least one being other than H; and
Z is H or 1-4C alkyl).

USES
Cpds. (I) have immunomodulating activity, including immunosuppressive and immunostimulating activities, and so are useful for treating autoimmune diseases, allergic conditions, cancer, bacterial infections, etc. Dose is 0.1-100 mg/kg parenterally daily or 0.001-1 g/kg orally daily.

PREPARATION
Methods used include:
(1) reaction of an amino-protected glutamic acid anhydride with a YO-CO-X-substd. aniline (II) (Y is 1-4C alkyl), then the protecting gp. is eliminated. The protecting gp. for the $NH_2$ may include incorporation in a phthalimido gp.;
(2) reaction of glutamic acid, having the α-COOH and α-$NH_2$ protected, with (II) in the presence of an activating agent; then protecting gps. are removed; and
(3) reaction of a reactive deriv. at the γ-carboxyl of glutamic acid, having the α-COOH and α-$NH_2$ protected, with (II); then protecting gps. are removed.

EXAMPLE
74.28 g N-benzyloxycarbonyl-L-glutamic acid α-benzyl ester and 28 ml $NEt_3$ were added to a mixt. of 250 ml THF and 250 ml DMF. The mixt. was stirred with ice-cooling and 26.4 ml ClCOOiBu was added dropwise. The mixt. was stirred for 15 mins., then 35.84 g Et p-aminophenylacetate in 50 ml DMF was added and the mixt. stirred for 30 mins., with ice cooling, then for 8 hrs. at room temp. The solvent was evapd. and the residue purified to give an intermediate, which was catalytically hydrogenated (Pd black) in aq. EtOH to give N-(4-ethoxycarbonylmethylphenyl)glutamate, m.pt. 179.8-180.5°C.(69pp1248).
(E)ISR:- J55026870 GB2034690 US4167449 J55036428 J55036454 3.Jnl.Ref

B(10-B2E, 12-A1, 12-A6, 12-D2, 12-G7) 4 32

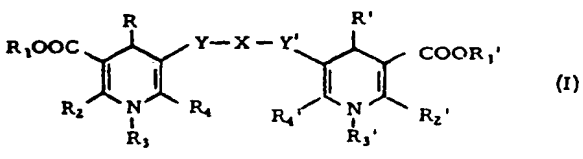
EP--52296+

4113 E/22 B03 FARB 13.11.80
FARBENFABR BAYER AG *EP--52-300
13.11.80-DE-042769 (26.05.82) A61k-31/44 C07d-211/90 C07d-401/14 C07d-405/14 C07d-409/14 C07d-413/14

**3-Linked 4-aryl-1,4-dihydro-pyridine-3 carboxylic acid derivs. - with cardiovascular e.g. antihypertensive, vasodilator, cerebral or coronary activity**

D/S: E(AT BE CH DE FR GB IT LI LU NL SE)

C3-linked 4-aryl-1,4-dihydro-pyridine-3-carboxylic acid derivs. of formula (I) and their salts are new.



(I)

(R and R' are aryl, thienyl, furyl, pyrryl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, naphthyl, quinolyl, isoquinolyl, indolyl, benzimidazolyl, quinazolyl or quinoxalyl all opt. mono-, di- or trisubstd. by phenyl, alkyl, alkenyl, alkoxy, alkenyloxy, alkylene, dioxyalkylene, halogen, mono- or polyfluoroalkyl, mono- or polyfluoro-alkoxy, OH, $NH_2$, alkylamino, $NO_2$, CN, $N_3$, COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl and $SO_2$-alkyl;
$R_1$ and $R_1'$ are opt. branched or cyclic, opt. unsatd. hydrocarbon residues opt. interrupted by 1 or 2 O and opt. substd. by halogen or OH or by phenyl, phenoxy, phenylthio or phenylsulphonyl (all opt. substd. by halogen, CN, dialkylamino, alkoxy, alkyl, $CF_3$ or $NO_2$);
$R_2$, $R_2'$, $R_4$ and $R_4'$ are H or an opt. cyclic, opt. unsatd. hydrocarbon residue opt. substd. by halogen, OH, aryl or amino (opt. substd. by opt. substd., opt. cyclic, opt. unsatd. hydrocarbyl);
$R_3$ and $R_3'$ are H, opt. substd. aryl or aralkyl, or opt. substd. alkyl the chain of which may be interrupted by 1 or 2 O;
Y and Y' are -CO-O-, CONH, CO-S, CO or $SO_2$;
X is a bridging gp. with ⩾ 1 $CH_2$ and ⩽ 9 adjacent $CH_2$, the bridging gp. also contg. (in any order) 1-5 chain members selected from O, S, SO, $SO_2$, CO, CS, $NR_5$, $C(R_6)_2$, $C(R_6)=C(R_6)$; C≡C, CH=CH, CH=N, arylene, heteroarylene, cycloalkylene, cycloalkenylene, piperazinylene, piperidylene, pyrrolidinylene and morpholinylene;
$R_5$ is H, alkyl or aralkyl; and

B(6-H, 7-D4, 12-C10, 12-E1, 12-F1, 12-F5, 12-F7) 5 33

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